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PATENT SPECIFICATION

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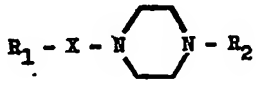
COMPLETE SPECIFICATION

Novel N,N'-Disubstituted Piperazine Compounds and their preparation

We, SOCIETE INDUSTRIELLE POUR LA FABRICATION DES ANTIBIOTIQUES (S.I.F.A.) of 67 boulevard Haussmann, Paris (8°) France, a body corporate organised under the laws of France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new piperazine derivatives which can be used as therapeutic substances or employed for the preparation of such substances, and also the process for the preparation of such derivatives. The new derivatives provided by the present invention correspond to the general formula:



(1)

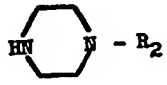
in which R_1 represents a phenyl, 4 - methoxyphenyl or 3,4 - dimethoxyphenyl radical, R_2 represents a 2 - pyridyl, phenyl 2-halogenophenyl, 2 - alkoxyphenyl or 2 - alkylphenyl radical, the alkyl and alkoxy radicals containing 1 to 3 carbon atoms and X represents a divalent saturated aliphatic hydrocarbon radical, which is linear or branched and contains 3 or 4 carbon atoms.

The compounds corresponding to the above general formula (1) are of basic character and their acid addition salts with mineral or organic acids are also novel.

The compounds of the general formula (1) can be prepared by reacting a halide of the general formula

$$R_1—X—Hal$$

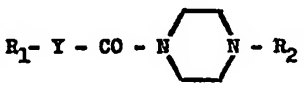
with a substituted piperazine of the general formula:



(R_1, R_2 and X having the meaning defined above and Hal being a halogen atom), in the presence of an alkaline agent capable of fixing the hydrohalic acid formed during the reaction. It is preferred to operate in the presence of an inert organic solvent and, if desired at the boiling point of the solvent. The solvent is so chosen that the halide formed by the action of the alkaline agent on the hydrohalic acid is insoluble therein. After eliminating this halide, the desired substance is then isolated from the liquid phase by the usual means. According to one embodiment of the process excess of the substituted piperazine is used as alkaline agent, or a mineral substance endowed with basic properties is used as an agent.

The substances of the general formula (1), of which the carbon atom of X bonded to the nitrogen of the piperazine is part of a methylene radical, can be prepared by a 2-stage process.

In a first stage, substances of the general formula:



(2)

are prepared, in which R_1 and R_2 have the

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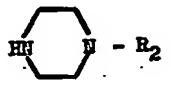
meaning defined above and Y represents a linear or branched divalent aliphatic hydrocarbon radical, which may or may not be saturated and which contains 2 or 3 carbon atoms, and then in a second stage, these compounds are reduced by conventional processes.

The derivatives of the general formula (2) can be prepared in various ways:

a) a piperazine of the general formula:



(3)

can be reacted with an acid of the general formula:

$$R_1—Y—COOH$$

R_1, R_2 and Y being as defined above, in a reaction medium which permits the elimination of the water formed during the reaction. It is preferred to work in an inert organic solvent which may be brought to boiling point. In one particular non-limitative form of the invention, use is made of a solvent capable of forming an azeotrope with the water formed during the condensation. Aromatic or aliphatic hydrocarbons or a halide thereof can be used as solvent. When the theoretical quantity of water has been removed, the desired compound is isolated by the usual means of purification and isolation.

b) A piperazine of the general formula (3) is reacted with an acid halide of the general formula:

$$R_1—Y—CO—Hal$$

R_1 and Y being as defined above and Hal representing a halogen atom, in the presence of an alkaline agent capable of fixing the hydrohalic acid formed during the reaction. It is preferred to work in an inert organic solvent which may be brought to boiling point and which is so chosen that the halide formed by the action of the alkaline agent on the hydrohalic acid is insoluble therein. After eliminating this halide, the desired substance is then isolated from the liquid phase by the usual means. According to one method of carrying out the invention, excess of the substituted piperazine or a mineral substance having basic properties is preferably used as alkaline agent.

c) A piperazine of the general formula (3) is reacted with an acid anhydride of the general formula:

$$(R_1—Y—CO)_2O$$

R_1 and Y being as defined above, in the presence of an alkaline agent capable of fixing the organic acid which is formed. It is preferred to work in the presence of an inert organic solvent which may be brought to boiling point and which is so chosen that the organic salt which is formed is insoluble therein. After removing this salt, the desired substance is then isolated from the liquid phase by the usual means. The alkaline agent used according to the process can either be the substituted piperazine used in excess, or a mineral substance having basic properties.

d) A piperazine of the general formula (3) is reacted with an ester of the general formula:

$$R_1—Y—CO.OA$$

A being a low alkyl radical having from 1 to 4 carbon atoms, R_1 and Y being as defined above, in a reaction medium permitting the removal of the alcohol AOH formed during the reaction. It is preferred to work in an inert organic solvent which may be brought to boiling point. In one particular non-limitative form of the invention, a solvent is used which is capable of forming an azeotrope with the alcohol which has formed such as an aromatic or aliphatic hydrocarobn or halide thereof. When the alcohol has been removed, the desired compound is isolated by the usual means of purification and isolation. It is also possible, when carrying out the process, to add a metal alcoholate catalyst, such as aluminium isopropylate, to the reaction medium.

The second stage in the process for preparing compounds of the general formula (1) of which the carbon atom of Y connected to the nitrogen atom of the piperazine ring is a methylene radical, is characterised by bringing together a substance of the general formula (2) and a complex metal hydride such as the double hydride of lithium and aluminium. It is preferred to work in an anhydrous and non-hydroxylated inert organic solvent, which may be brought to boiling point. The product obtained is then decomposed by the action of water and the desired substance is purified and separated by the usual means.

In one particular form of the process described above, the substances of the general formula (1) can be prepared by reduction of the substances of the general formula (2), the reduction being carried out directly in the reaction medium for forming the substances of general formula (2) without isolating the latter.

Salts can be obtained from basic substances of the general formula (1) by reaction with the corresponding organic or mineral acids.

The derivatives provided by the present invention have interesting pharmacodynamic properties and for this reason constitute valuable therapeutic agents. In particular, they are adrenolytics, hypotensors, potentiators of

barbiturates and depressants of the central nervous system and, for this reason are capable of being used in medicine for human beings in the treatment of illnesses such as hypertension and anxiety states.

The approximate acute toxicity of the derivatives according to the invention has been studied in connection with mice by intraperitoneal administration. The experiments were carried out on a restricted number of animals and the results are either expressed by two figures, of which the smaller is the LD 0 and the larger is the LD 100, or expressed by a single figure corresponding to the LD 50.

The depressant effect on the central nervous system has been estimated by the traction test (Courvoisier, J. Clin, Exper. Psychopharmacol. 1956, 17—28) and the chimney test. According to this latter test, a mouse is watched while climbing backwards in a vertically disposed glass tube. A normal mouse should climb in less than 10 seconds, while a mouse subjected to the action of a depressant of the central nervous system climbs in a time which is longer than 10 seconds. (The derivatives of the invention were administered to the animals intraperitoneally).

The potentialising activity of barbiturates was also studied by injecting 0.025 g./kg. of sodium mebubarbital into the animals 35 minutes after the derivatives being studied were administered.

The adrenolytic activity was investigated on the isolated seminal vesicle of a guinea pig under the following conditions:

—oxygenated Locke bath at 39°C.

adrenalin: 100 mcg/50 ml. for 1 minute

—derivatives studied: contact for 4 minutes.

The results are expressed in inhibitive concentrations 50% (I.C. 50).

The action of the derivatives on the arterial pressure were investigated, in respect of certain of the derivatives described, on a dog after administration intrasaphenally.

All the results obtained from these various experiments are set out at the end of the corresponding Examples.

The novel derivatives provided by the invention can be used therapeutically either in the form of the base, or in the form of pharmaceutically acceptable addition salts, for example the salts obtained with sulphuric, hydrochloric, hydrobromic, phosphoric, acetic, maleic, citric, tartaric, salicyclic, benzoic and cinnamic acids. The active therapeutic doses vary according to the subjects, the gravity of the cases, the method of administration and the effect which is desired. Generally speaking, the useful dosology for a human being is between 0.020 g. and 1 g. per day.

The present invention is also concerned with solid or liquid pharmaceutical compositions for oral, rectal or parenteral administration, comprising one or more of the derivatives of the formula (1) used in the form of a base or salt. As well as the active therapeutic product or products, these compositions contain one or more of the excipients usually employed in such preparations, such as starch, calcium carbonate, alginic acid, lactose, magnesium stearate, cocoa butter, aqueous or non-aqueous liquid vehicles, vegetable oils, wetting agents, dispersing agents and emulsifiers. The compositions intended for parenteral administration are sterilised by using the conventional sterilisation methods.

The following non-limiting Examples further illustrate the present invention:

EXAMPLE 1

A mixture of 20 g. of 3 - phenyl - propyl bromide, 21.6 g. of N - (2 - chlorophenyl)-piperazine and 15.2 g. of anhydrous potassium carbonate in 200 cc. of butanol is heated for 20 hours to 100 to 110°C. while stirring. After cooling, the mineral salts are separated by centrifuging, the butanol is driven off and 23 g. of N - (3 - phenyl - propyl) - N¹ - (2-chlorophenyl) - piperazine are obtained by distillation. (Yield 73%; Boiling Point under 0.05 mm. of mercury 175°C.).

The hydrochloride of this base is obtained by the conventional means. After recrystallisation from water, it melts at 190 to 195°C. on a microscope provided with a heating stage.

Analysis: C_{19} H_{24} Cl_2 N_2

	C.	H.	Cl. mineral
Calculated %	64.95	6.89	10.1
Found %	64.9	6.9	10.1

The LD 50 is between 100 mg./kg. and 200 mg./kg.

EXAMPLE 2

A mixture of 23 g. of 3 - (4 - methoxyphenyl) - propyl bromide and 32.6 g. of N-(2-pyridyl) - piperazine in 250 cc. of anhydrous xylene are refluxed for 20 hours. After cooling, the N - (2 - pyridyl) - piperazine hydrobromide which is formed is centrifuged, the xlyene phase is concentrated and the dry

extract is crystallised directly. There are obtained 20.8 g. of N - [3 - (4 - methoxyphenyl) - propyl] - N^1 - (2 - pyridyl) - piperazine, after crystallisation from petroleum ether. (Yield 67%; Melting Point on a microscope provided with a heating stage is 47°C.).

Analysis: $C_{19}H_{23}N_3O$

	N.
Calculated %	13.49
Found %	13.6

The LD 50 is between 200 mg./kg. and 400 mg./kg. Depressant effect on the central nervous system of a mouse: from 50 mg./kg. Adrenolytic activity: for an I.C. 50 of 1.10^{-5}.

With a dog: sustained hypotension and inversion of the adrenaline effects from 0.5 mg./kg.

The LD 50 is between 100 mg./kg. and 200 mg./kg. Adrenolytic activity for an I.C. of 2.10^{-5}.

With a dog: sustained hypotension from 1 mg./kg. and cancellation of the effects of adrenaline from 2 mg./kg.

EXAMPLE 5

A solution of 23 g. of 3 - (4 - methoxyphenyl) - propyl bromide and 32.6 g. of N - phenyl - piperazine in 300 cc. of anhydrous xylene is boiled under reflux for 20 hours while stirring. After cooling, the N-phenyl - piperazine hydrobromide formed is separated by centrifuging. By concentration and distillation of the xylene phase, there is obtained an oil which is dissolved in ethanol to which a solution of hydrochloric acid in ethanol is added: a white precipitate is formed which is recrystallised from water. 20.3 G. of N - [3 - (4 - methoxyphenyl)-propyl] - N^1 - phenyl piperazine hydrochloride are obtained. (Yield 58%; Melting Point on a microscope provided with a heating stage is 160°C.).

Analysis: $C_{20}H_{27}ClN_2O$

	Cl.	N.
Calculated %	10.25	8.07
Found %	10.4	8.15

LD 50:200 mg./kg. Depressant effect on the central nervous system of a mouse: from 25 mg./kg. Adrenolytic activity for an I.C. 50 of 1.10^{-7}.

EXAMPLE 3

N - (1 - phenyl - 2 - propyl) - N^1 - phenyl-piperazine which can be crystallised from petroleum ether (fraction 35 to 50°C.) is obtained in a similar manner in a yield of 49%. Melting Point on a microscope provided with a heating stage is 41°C.

Analysis: $C_{19}H_{24}N_2$

	C.	H.
Calculated %	81.38	8.63
Found %	81.5	8.5

EXAMPLE 4

N - (1 - phenyl - 4 - butyl) - N^1 - (2-pyridyl) - piperazine is obtained in a similar way in a yield of 52%. (Melting Point on a microscope provided with a heating stage is 35 to 36°C.).

Analysis: $C_{19}H_{25}N_3$

	C.	H.
Calculated %	77.25	8.53
Found %	77.05	8.35

The LD 50 is between 200 mg./kg. and 400 mg./kg. Marked depressant effect in the central nervous system of a mouse from a dose of 50 mg./kg. Adrenolytic activity for an I.C. 50 of 2.10^{-7}.

EXAMPLE 6

Using the method described in Example 5, and starting with 5.2 g. of 3 - (3,4 - dimethoxyphenyl) - propyl bromide and 6.48 g. of N-phenyl piperazine, there are obtained 4.55 g. of N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N¹ - phenyl - piperazine dihydrochloride which is crystallised from methanol. (Yield 55%; Melting Point on a microscope provided with a heating stage is 173 to 174°C.).

Analysis: $C_{21}H_{30}Cl_2N_2O_2$

	Cl.
Calculated %	17.20
Found %	17.2

The LD 50 is between 200 mg./kg. and 400 mg./kg. Marked depressant activity on the central nervous system of a mouse from a dose of 50 mg./kg. Adrenolytic activity for an I.C. 50 of 2.10^{-7}.

EXAMPLE 7

Using the method described in Example 5, starting with 5.2 g. of 3 - (3,4 - dimethoxyphenyl) - propyl bromide and 6.52 g. of N-(2 - pyridyl) - piperazine, there are obtained 6.6 g. of N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N¹ - (2 - pyridyl) - piperazine dihydrochloride which is crystallised from absolute ethanol. (Yield 80%; Melting Point on a microscope provided with a heating stage is 203°C.).

Analysis: $C_{20}H_{29}Cl_2N_3O_2$

	C.	H.
Calculated %	57.96	7.05
Found %	57.8	7.1

LD 50: 200 mg./kg. Depressant activity on the central nervous system of a mouse: from a dose of 25 mg./kg. Adrenolytic activity for an I.C. 50 of 2.10^{-7}.

EXAMPLE 8

Using the method described in Example 5, starting with 13 g. of 1 - (3,4 - dimethoxyphenyl) - 2 - propyl bromide and 16.2 g. of N - phenyl - piperazine, there are obtained 10.15 g. of N - [1 - (3,4 - dimethoxyphenyl)-2 - propyl] - N¹ - phenyl - piperazine hydrochloride which is crystallised from a mixture of methanol and ether. (Yield 54%; Melting Point on a microscope provided with a heating stage is 197 to 198°C.).

Analysis: $C_{21}H_{30}Cl_2N_2O_2$

	Cl.
Calculated %	17.16
Found %	17.3

The LD 50 is between 100 mg./kg. and 200 mg./kg. Depressant activity on the central nervous system of a mouse: from a dose of 25 mg./kg. Adrenolytic activity for an I.C. 50 of 1.10^{-8}.
With a dog: sustained hypotension and inversion of the adrenaline effects from the dose of 0.5 mg./kg.

EXAMPLE 9

Using the working method described in Example 5, starting with 21.3 g. of 1-phenyl-3 - bromobutane and 32.6 g. of N - (2-pyridyl) - piperazine, there are obtained 24.7 g. of N - (1 - phenyl - 3 - butyl) - N¹ - (2-pyridyl) - piperazine dihydrochloride which is crystallised from isopropanol.
(Yield 67%; Melting Point on a microscope provided with a heating stage is 190°C.).

Analysis: $C_{19}H_{27}Cl_2N_3$

	C.	H.
Calculated %	61.95	7.39
Found %	61.8	7.6

LD 50: 200 mg./kg. Adrenolytic activity for an I.C. 50 of 2.10^{-7}
With a dog: sustained hypotension from a dose of 1 mg./kg. and cancellation of the effects of adrenaline from the dose of 5 mg./kg.

EXAMPLE 10

A. First of all, the N - [3 - (3,4 - dimethoxyphenyl) - propionyl] - N^1 - (2 - chlorophenyl) - piperazine is prepared by heating 22 g. of 3 - (3,4 - dimethoxyphenyl)-propionic acid and 19.65 g. of N - (2 - chlorophenyl)-piperazine in 150 cc. of xylene to boiling point, the water being removed as it is formed. When this elimination of the water is complete, the heating is stopped, the substance allowed to cool, the xylene is concentrated and the residue is crystallised from isopropyl ether. 28 g. of N - [3 - (3,4 - dimethoxyphenyl) - propionyl] - N^1 - (2 - chlorophenyl)-piperazine in crystallised form are obtained. (Yield 72%; Melting Point on a microscope provided with a heating stage is 81°C.).

Analysis: C_{21} H_{25} Cl N_2 O_3

	C.	H.
Calculated %	64.85	6.48
Found %	64.75	6.6

B. A solution of 0.1 molecule of lithium aluminium hydride in 250 cc. of anhydrous ether is then prepared. 19.4 G. of N - [3-(3,4 - dimethoxyphenyl)propionyl] - N^1 - (2-chlorophenyl) - piperazine in solution in 100 cc. of a mixture of equal volumes of anhydrous benzene and anhydrous ether are slowly introduced. The mixture is left boiling under reflux for 4 hours while stirring, whereupon it is cooled and hydrolysed in the conventional manner. After drying, concentration of the organic solution and crystallisation of the dry extract from isopropanol, there are obtained 14.8 g. of N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N^1 - (2 - chlorophenyl) - piperazine in crystallised form. (Yield 79%; Melting Point on microscope provided with a heating stage is 55°C.).

Analysis: C_{21} H_{27} Cl N_2 O_2

	C.	H.
Calculated %	67.27	7.26
Found %	67.5	7.3

The LD 50 is between 200 mg./kg. and 400 mg./kg. The depressant activity on the central nervous system of a mouse: from a dose of 50 mg./kg. Adrenolytic activity for an I.C. 50 of 5.10^{-7}.
With a dog: sustained hypotension from 1 mg./kg. and inversion of the effects of adrenaline from 2 mg./kg.

EXAMPLE 11

A.—First of all, N - (3,4 - dimethoxycinnamoyl) - N^1 - (2 - methoxyphenyl)-piperazine is prepared according to the process described in Example 10 A., starting with 21.8 g. of 3,4 - dimethoxycinnamic acid and 19.2 g. of N - (2 - methoxyphenyl) - piperazine in 150 cc. of xylene. There are obtained 24 g. of N - (3,4 - dimethoxycinnamoyl)-N^1 - (2 - methoxyphenyl) - piperazine after crystallisation from ethyl acetate. (Yield 63%; Melting Point on a microscope provided with a heating stage is 119°C.).

Analysis: C_{22} H_{26} N_2 O_4

	C.	H.
Calculated %	69.09	6.85
Found %	68.9	6.8

B.—Thereafter, using the method described in Example 10 B., and starting with 0.2 molecule of lithium aluminium hydride and 19.2 g. of N - (3,4 - dimethoxycinnamoyl) - N^1 - (2 - methoxyphenyl) - piperazine, there are obtained 7.8 g. of N - [3 - (3,4 - dimethoxyphenyl) - propyl] - N^1 - (2 - methoxyphenyl)-piperazine after crystallisation from 96% ethancl. (Yield 43%; Melting Point on a microscope provided with a heating stage is 102 to 103°C.).

Analysis: C_{22} H_{30} N_2 O_3

	C.	H.
Calculated %	71.32	8.16
Found %	71.2	8.15

LD 50: 100 mg./kg. Depressant effect on the central nervous system of a mouse: from the dose of 12 mg./kg.

EXAMPLE 12

A. First of all, N - (4 - phenyl - butyryl)-N^1 - (2 - chlorophenyl) - piperazine is prepared according to the process described in Example 10A., starting with 17.6 g. of 4-phenyl - butyric acid and 19.65 g. of N - (2-chlorophenyl) - piperazine in 100 cc. of xylene. There are obtained 28.6 g. of N - (4 - phenyl-butyryl) - N^1 - (2 - chlorophenyl) - piperazine after crystallisation from isopropyl ether. (Yield 82%; Melting Point on a microscope provided with a heating stage is 35 to 36°C.).

Analysis: C_{20} H_{23} Cl N_2 O

	C.	H.
Calculated %	70.06	6.76
Found %	70.1	6.7

B. Thereafter, using the method described in Example 10 B., and starting with 0.1 molecule of lithium aluminium hydride and 17.1 g. of N - (4 - phenyl - butyryl) - N^1 - (2-chlorophenyl) - piperazine, there are obtained 10 g. of N - (4 - phenyl - butyl) - N^1 - (2-chlorophenyl) - piperazine. (Yield 60%; Melting Point on a microscope provided with a heating stage is 48°C.).

Analysis: $C_{20}H_{25}ClN_2$

	N.
Calculated %	8.53
Found %	8.5

The LD 50 is between 200 mg./kg. and 400 mg./kg. The depressant effect on the central nervous system is very marked with a mouse from a dose of 50 mg./kg. Adrenolytic activity for an I.C. 50 to 5.10^{-3}.

With a dog: Cancellation of the effects of adrenalin from the dose of 2 mg./kg.

EXAMPLE 13

A First of all, N - 4 - (4 - methoxyphenyl)-butyryl - N^1 - (2 - chlorophenyl) - piperazine is prepared by the process described in Example 10 A., starting with 10.7 g. of 4-(4 - methoxyphenyl) - butyric acid and 10.8 g of N - (2 - chlorophenyl) - piperazine in 80 cc. of xylene.

There are obtained 18 g. of N - [4 - (4-methoxyphenyl) - butyryl] - N^1 - (2 - chlorophenyl) - piperazine after crystallisation from hexane. (Yield 88%; Melting Point on a microscope provided with a heating stage is 65 to 66°C.).

Analysis: C_{21} H_{25} Cl N_2 O_2

	C.	H.	Cl.
Calculated %	67.63	6.78	9.51
Found %	67.6	6.8	9.5

B. Thereafter, using the method described in Example 10 B., and starting with 0.1 molecule of lithium aluminium hydride and 18.6 g. of N - [4 - (4 - methoxyphenyl)-butyryl] - N^1 - (2 - chlorophenyl) - piperazine, a white precipitate is obtained by addition of a solution of dry hydrochloric acid in absolute ethanol to the dehydrated organic solution, and this precipitate after recrystallisation from absolute ethanol, gives 18 g. of N - [4 - (4 - methoxyphenyl) - butyl] - N^1 - (2 - chlorophenyl)-piperazine hydrochloride. (Yield 91%; Melting Point on a microscope provided with a heating stage is 188°C.).

Analysis: $C_{21}H_{28}Cl_2N_2O$

	Cl mineral
Calculated %	8.97
Found %	9.0

The LD 50 is between 400 mg./kg. and 800 mg./kg. The depressant activity on the central nervous system is very marked with a mouse from a dose of 100 mg./kg. Adrenolytic activity for an I.C. 50 of 1.10^{-4}.

With a dog: sustained hypotension from 1 mg./kg. and inversion of the effects of adrenalin from 5 mg./kg.

EXAMPLE 14

A. First of all, N - [4 - (3,4 - dimethoxyphenyl) - butyryl] - N^1 - (2 - chlorophenyl)-piperazine is prepared according to the process described in Example 10 A., starting with 23.6 g. of 4 - (3,4 - dimethoxyphenyl)-butyric acid and 19.65 g. of N - (2 - chlorophenyl) - piperazine in 200 cc. of xylene, there are obtained 22.5 g. of N - [4 - (3,4 - dimethoxyphenyl) - butyryl] - N^1 - (2 - chlorophenyl) - piperazine after crystallisation from hexane. (Yield 55%; Melting Point on a microscope provided with a heating stage is 78 to 79°C.).

Analysis: $C_{22}H_{27}ClN_2O_3$

	C.	H.
Calculated %	65.58	6.76
Found %	65.8	6.9

B. Thereafter, using the method described in Example 10 B., and starting with 0.1 molecule of lithium-aluminium hydride and 18.4 g. of N - [4 - (3,4 - dimethoxyphenyl)-butyryl] - N^1 - (2 - chlorophenyl) - piperazine, there are obtained 10 g. of N - [4 - (3,4 - dimethoxyphenyl) - butyl] - N^1 - (2 - chlorophenyl) - piperazine after crystallisation from heptane. (Yield 56%; Melting Point on a microscope provided with a heating stage is 70°C.).

Analysis: $C_{22}H_{29}ClN_2O_2$

	C.	H.
Calculated %	67.94	7.52
Found %	67.9	7.6

The LD 50 is between 400 mg./kg. and 800 mg./kg. The depressant activity on the central nervous system is very marked with a mouse from a dose of 100 mg./kg. Adrenolytic activity for an I.C. 50 of 5.10^{-4}.

With a dog: sustained hypotension from 0.5 mg./kg. and greatly strengthened for 2 mg./kg.; inversion of the effects of adrenalin for 2 mg./kg.

EXAMPLE 15

Using the method described in Example 10 A., and starting with 12.05 g. of 4 - (3,4-dimethoxyphenyl) - butyric acid and 9.6 g. of N - (2 - methoxyphenyl) - piperazine in 100 cc. of xylene, 0.9 cc. of water are distilled after 20 hours. After direct reduction of the above xylene solution with 0.1 molecule of lithium-aluminium hydride using the working method described in Example 10 B., there are obtained 10.7 g. of N - [4 - (3,4 - dimethoxy - phenyl) - butyl] - N^1 - (2 - methoxyphenyl) - piperazine after crystallisation from isopropyl ether. (Yield 56%; Melting Point on a microscope provided with a heating stage is 89 to 91°C.).

The hydrochloride thereof is prepared by dissolving 8 g. of the base in 20 cc. of absolute ethanol and adding 10 cc. of 7%

anhydrous hydrochloric ethanol thereto. The hydrochloride precepitates by cooling and it is recrystallised from absolute ethanol. (Melting Point is 202°C.).

Analysis: C_{23} H_{33} Cl N_2 O_3

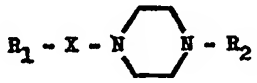
	C.	H.
Calculated %	65.62	7.90
Found %	65.3	7.8

The LD 50 is between 100 mg./kg. and 200 mg./kg. Marked depressant effect on the central nervous system of a mouse: from 25 mg./kg. Adrenolytic activity for an LC. 50 of 1.10^{-8}.

With a dog: inversion of the effects of adrenalin for 0.5 mg./kg.

WHAT WE CLAIM IS:—

1. Piperazine derivatives of the general formula:



(1)

and acid addition salts thereof, in which R_1 represents a phenyl, 4 - methoxyphenyl or 3,4 - dimethoxyphenyl radical, R_2 represents a 2-pyridyl, phenyl, 2 - halogenophenyl, 2-alkoxyphenyl or 2 - alkylphenyl radical, the alkyl and alkoxy radicals containing 1 to 3 carbon atoms, and X represents a linear or branched divalent saturated aliphatic hydrocarbon radical containing 3 or 4 carbon atoms.

2. N - (3 - phenyl - propyl) - N^1 - (2-chlorophenyl) - piperazine and acid addition salts thereof.

3. N - [3 - (4 - methoxyphenyl) - propyl]-N^1 - (2 - pyridyl) - piperazine and acid addition salts thereof.

4. N - (1 - phenyl - 2 - propyl) - N^1-phenyl - piperazine and acid addition salts thereof.

5. N - (1 - phenyl - 4 - butyl) - N^1 - (2-pyridyl) - piperazine and acid addition salts thereof.

6. N - [3 - (4 - methoxyphenyl) - propyl]-N^1 - phenyl - piperazine and acid addition salts thereof.

7. N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N^1 - phenyl - piperazine and acid addition salts thereof.

8. N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N^1 - (2 - pyridyl) - piperazine and acid addition salts thereof.

9. N - [1 - (3,4 - dimethoxyphenyl) - 2-propyl] - N^1 - phenyl - piperazine and acid addition salts thereof.

10. N - (1 - phenyl - 3 - butyl) - N^1 - (2-pyridyl) - piperazine and acid addition salts thereof.

11. N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N^1 - (2 - chlorophenyl) - piperazine and acid addition salts thereof.

12. N - [3 - (3,4 - dimethoxyphenyl)-propyl] - N^1 - (2 - methoxyphenyl) - piperazine and acid addition salts thereof.

13. N - (4 - phenyl - butyl) - N^1 - (2-chlorophenyl) - piperazine and acid addition salts thereof.

14. N - [4 - (4 - methoxyphenyl) - butyl]-N^1 - (2 - chlorophenyl) - piperazine and acid addition salts thereof.

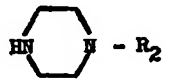
15. N - [4 - (3,4 - dimethoxyphenyl)-butyl] - N^1 - (2 - chlorophenyl) - piperazine and acid addition salts thereof.

16. N - [4 - (3,4 - dimethoxyphenyl)-butyl] - N^1 - (2 - methoxyphenyl) - piperazine and acid addition salts thereof.

17. A process for the preparation of the piperazine derivatives claimed in claim 1, which comprises reacting a halide of the general formula:

$$R_1—X—Hal$$

with a substituted piperazine of the general formula:

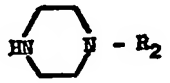


(2)

in which R_1, R_2 and X have the meanings given in claim 1 and Hal represents a halogen atom, in the presence of an alkaline agent capable of fixing the hydrohalic acid formed during the reaction.

18. A process as claimed in claim 17, wherein the alkaline agent is an excess of substituted piperazine or a mineral substance having basic properties.

19. A process for the preparation of the compounds claimed in claim 1, in which the carbon atom of X bonded to the nitrogen atom of the piperazine is part of a methylene radical, which comprises reacting a substituted piperazine of the general formula:



with an acid of the general formula

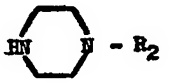
$$R_1—Y—COOH$$

(in which formulae R_1 and R_2 have the meanings given in claim 1 and Y represents a saturated or unsaturated linear or branched divalent aliphatic hydrocarbon radical containing 2 or 3 carbon atoms) in a reaction medium which permits the elimination of the water formed during the reaction, then reacting the intermediate obtained with a double metal hydride and subsequently treating with water.

20. A process as claimed in claim 19 wherein the reaction medium which permits the elimination of the water is an inert solvent, which may be brought to boiling point.

21. A process as claimed in claim 20 wherein the inert solvent is capable of forming an azeotrope with water.

22. A process for the preparation of the compounds claimed in claim 1, in which the carbon atom of X bonded to the nitrogen atom of the piperazine is part of a methylene radical, which comprises reacting a substituted piperazine of the general formula:

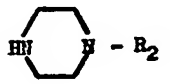


with an acid halide of the general formula

$$R_1—Y—CO—Hal$$

(in which formulae R_1 and R_2 have the meanings given in claim 1, Y represents a saturated or unsaturated linear or branched divalent aliphatic hydrocarbon radical containing 2 or 3 carbon atoms and Hal represents a halogen atom) in the presence of an alkaline agent capable of fixing the hydrohalic acid which is formed, then reacting the intermediate obtained with a double metal hydride and subsequently treating with water.

23. A process for the preparation of the compounds claimed in claim 1, in which the carbon atom of X bonded to the nitrogen atom of the piperazine is part of a methylene radical, which comprises reacting a substituted piperazine of the general formula:

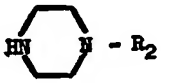


with an acid anhydride of the general formula

$$(R_1—Y—CO)_2O$$

(in which formulae R_1 and R_2 have the meanings given in claim 1 and Y represents a saturated or unsaturated linear or branched divalent aliphatic hydrocarbon radical containing 2 or 3 carbon atoms) in the presence of an alkaline agent, then reacting the intermediate obtained with a double metal hydride and subsequently treating with water.

24. A process for the preparation of the compounds claimed in claim 1, in which the carbon atom of X bonded to the nitrogen atom of the piperazine is part of a methylene radical, which comprises the steps of reacting a substituted piperazine of the general formula:



with an ester of the general formula:

$$R_1—Y—CO.OA$$

(in which formulae R_1 and R_2 have the meanings given in claim 1, Y represents a saturated or unsaturated linear or branched divalent aliphatic hydrocarbon radical containing 2 or 3 carbon atoms and A represents an alkyl radical containing from 1 to 4 carbon atoms) in a reaction medium which permits the elimination of the alcohol A—OH formed, then reacting the intermediate formed with a double metal hydride and subsequently treating with water.

25. A process as claimed in claim 24, wherein the reaction medium which permits the elimination of the alcohol A—OH formed is an inert solvent which may be brought to boiling point.

26. A process as claimed in claim 25, wherein the solvent is capable of forming an azeotrope with the alcohol.

27. A process as claimed in any of the claims 24 to 26, wherein the first step of the reaction is carried out in the presence of a metallic alcoholate as catalyst.

28. A process as claimed in claim 27, wherein the catalyst is aluminium isopropylate.

29. A process as claimed in any of the claims 19, 22, 23 or 24, wherein the double metal hydride is lithium aluminium hydride.

30. A process for the preparation of the compounds claimed in claim 1, substantially as described with reference to any of the Examples.

31. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 16 and an inert carrier.

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